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Treatment of limb synovial sarcoma with metastasis at presentation

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Abstract

Limb synovial sarcoma (LSS) patients with metastasis at presentation usually have a very poor prognosis. Little is known about survival prediction and risk factors in these patients owing to the condition's rarity. Thus, this study examined the survival and prognostic variables of metastatic LSS.

Clinical data for LSS patients with metastasis at presentation from 1975 to 2016 were obtained from the surveillance, epidemiology, and end results database. The Kaplan–Meier method was used to determine the survival curves. Univariate and multivariate Cox regression analysis were conducted to identify the prognostic predictors.

The study enrolled 217 patients. Male predominance was observed in the metastatic LSS group. The median age at diagnosis of this population was 40 years. The subtypes were "not otherwise specified" (49.8%), spindle cell (32.7%), biphasic (17.1%), and epithelioid cell (0.5%). The 3-year overall and cancer-specific survival rates of the entire group were 27.2% and 28.3%, respectively. Tumor size <10 cm, surgery, radiotherapy, and chemotherapy were independent predictors of improved overall and cancer-specific survival in the multivariate analyses.

Comprehensive treatment for LSS patients with metastasis at diagnosis is necessary and effective and can prolong survival.

Abbreviations: CSS = cancer-specific survival, ICD-O-3 = 3rd edition of International Classification of Diseases for Oncology, LSS = limb synovial sarcoma, OS = overall survival, SS = synovial sarcoma, SEER = surveillance, epidemiology, and end results.

Keywords: clinical feature, limb synovial sarcoma, metastasis, prognostic factor

1. Introduction

Synovial sarcoma (SS) is an aggressive mesenchymal neoplasm with distinct uniform cytopathological features.[1] It can occur almost anywhere and affects people of all ages, with a propensity to occur in adolescents and young adults.[2–4] SS accounts for 5% to 10% of soft tissue sarcomas in adolescents and young adults.[2,5,6] Most cases occur at extra-articular sites in the extremities.[7] The treatment for local SS includes wide resection and adjuvant or neoadjuvant radiotherapy, which provides a satisfactory prognosis.[8] Although SS is moderately sensitive to chemotherapy,[9,10] the use of chemotherapy remains controversial.[11,12] SS is regarded as a high-grade sarcoma, characterized by local invasiveness and metastatic propensity.[13] The lung is the most common site of SS metastasis.[6] Patients usually have a poor prognosis if they developed metastatic disease.[7] Metastatic limb synovial sarcoma (LSS) is very rare, with no standard therapy. However, the demographic, prognostic, and outcomes data of metastatic LSS are poorly documented.

Using the surveillance, epidemiology, and end results (SEER) database, we identified all patients diagnosed with LSS with metastasis at presentation from 1975 to 2016. This study first examined the clinical features of LSS patients with metastasis at presentation and confirmed the prognostic factors for this patient population, which should improve clinicians' understanding of this disease.

2. Patients and methods

2.1. Study population

The data for all patients diagnosed with LSS with metastasis at presentation between 1975 and 2016 were extracted from the SEER database (www.seer.cancer.gov), which is available to the public. This database collects data from 18 registry areas in the United States and does not contain patient identification information. The study was approved by the local Institutional Review Board.

LSS patients were selected based on the 3rd edition of the International Classification of Diseases for Oncology (ICD-O-3). ICD-O-3 codes 9040–9043 were used to identify SS patients, and primary site codes C40.0-C41.9 indicated extremity sites. All enrolled patients were confirmed pathologically without using the clinical diagnosis or autopsy findings. Only patients with

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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distant disease were included in this study. Patients lacking survival data were excluded. Clinicopathological characteristics obtained from the SEER database included age at diagnosis, gender, tumor grade, tumor type, tumor size, surgery, radiotherapy, chemotherapy, vital status, cause of death, and survival in months. Here, surgery or radiotherapy refers to local treatment of tumors located at the primary sites. Age was divided into <40 and ≥40 years. Tumor grade was divided into low grade, high grade, and unknown. Low grade refers to ICD-O-3 Grades 1 (well differentiated) and 2 (moderately differentiated); high grade refers to ICD-O-3 Grades 3 (poorly differentiated) and 4 (undifferentiated anaplastic).

2.2. Statistical analysis

We performed all statistical tests with SPSS 20.0. Following a previous study,[14] we defined overall (OS) and cancer-specific (CSS) survival as the times from diagnosis to death from any cause and from diagnosis to death due specifically to cancer, respectively. The Kaplan–Meier method was used to plot survival curves and predict survival rates. The log-rank test was applied to compare survival curves. To identify independent predictors of survival, univariate and multivariate Cox regression analyses were performed simultaneously. We also calculated hazard ratios with corresponding 95% confidence intervals to reveal the effect of various predictors on survival. Two-sided *P*-values < .05 were considered statistically significant.

3. Results

3.1. Characteristics of patients with LSS and metastasis at presentation

This study included 217 metastatic LSS patients for the prognostic analysis. Table 1 summarizes their basic clinical characteristics: 106 (48.8%) patients were aged <40 years, and 111 (51.2%) patients were aged ≥40 years. A total of 37.8% were female, and 62.2% male. Eleven (5.1%), 104 (47.9%), and 102 (47.0%) had low, high, and unknown tumor grade, respectively. Nearly half of the patients were diagnosed with SS not otherwise specified (49.8%). Tumor size was available in 163 cases (75.1%) and was ≥10 cm in nearly half the cases (47.0%). Roughly two-thirds of the patients (65.0%) underwent local surgery, 88 (40.6%) underwent radiotherapy, and 161 (74.2%) received chemotherapy. The 3-year OS and CSS rates were 27.2% and 28.3%, respectively.

3.2. Univariate analysis

Table 2 shows the median survival data of the metastatic LSS patients. In the univariate analyses (Table 3), age at diagnosis, gender, tumor grade, and tumor type were not significantly associated with either OS or CSS. Radiotherapy and chemotherapy were associated with OS, but not with CSS. Patients who underwent local surgery had significantly better outcomes than those who did not (Fig. 1). A tumor size <10 cm did not predict a better prognosis than a tumor size ≥10 cm.

3.3. Multivariate analysis

Variables with $P < .1$ from the univariate analyses were examined in the Cox multivariate analysis. Tumor size <10 cm, surgery, radiotherapy, and chemotherapy all showed significant survival benefits (Table 4).

Table 1

Characteristics of 217 patients with limb synovial sarcoma and metastasis at presentation.

Category	Value
Age, yr	
<40	106 (48.8%)
≥40	111 (51.2%)
Gender	
Female	82 (37.8%)
Male	135 (62.2%)
Tumor grade	
Low	11 (5.1%)
High	104 (47.9%)
Unknown	102 (47.0%)
Tumor type	
Synovial sarcoma, NOS	108 (49.8%)
Synovial sarcoma, spindle cell	71 (32.7%)
Synovial sarcoma, biphasic	37 (17.1%)
Synovial sarcoma, epithelioid cell	1 (0.5%)
Tumor size	
<10 cm	61 (28.1%)
≥10 cm	102 (47.0%)
Unknown	54 (24.9%)
Surgery	
Yes	141 (65.0%)
No	76 (35.0%)
Radiation treatment	
Yes	88 (40.6%)
No	129 (59.4%)
Chemotherapy	
Yes	161 (74.2%)
No	56 (25.8%)
Dead	
Yes	179 (82.5%)
No	38 (17.5%)
3-yr OS rate	27.2%
3-yr CSS rate	28.3%
5-yr OS rate	13.7%
5-yr CSS rate	13.2%

CSS = cancer-specific survival, NOS = not other specified, OS = overall survival.

4. Discussion

We performed a survival analysis of 217 metastatic LSS patients from the SEER database. Because metastatic LSS is rare, few studies have documented its outcomes. There is also no standard treatment for metastatic LSS. Knowledge of patient survival will help clinicians to develop appropriate surgical procedures. This study is the first to report the clinical features of metastatic LSS patients and to explore the independent predictors of survival using the public SEER database.

The average and median ages at diagnosis of this population were 40 years, which is similar to the 35.4 years reported by Krieg et al[15] Like SS, LSS tends to affect younger people.[8] In a single-center study, Spurrell et al[9] reported a slight male predominance in advanced SS and in a metastatic LSS group. Metastasis is common in LSS, and the lung is the most common site.[8] Despite treatment, SS has high recurrence (24%–29%) and metastasis (47%–48%) rates.[11,15,16] Furthermore, SS patients with metastasis at diagnosis had a significantly poorer OS than those with later metastasis.[15] The 5-year OS rate of this metastatic cohort was 13.7%, which was lower than the value reported by Krieg et al,[15] 22.5%, among SS patients with metastasis at diagnosis. That study included only 9 SS patients with metastasis

Table 2

Median survival data (month) of patients with limb synovial sarcoma and metastasis at presentation.

Category	OS	95% CI	CSS	95% CI
Overall	18.0±1.3	15.5–20.5	19.0±1.5	16.0–22.0
Age, yr				
<40	23.0±1.9	19.3–26.7	24.0±2.2	19.6–28.4
≥40	15.0±1.9	11.2–18.8	16.0±1.4	13.3–18.7
Gender				
Female	20.0±2.4	15.3–24.7	22.0±2.4	17.3–26.7
Male	18.0±1.3	15.4–20.6	19.0±1.3	16.5–21.5
Tumor grade				
Low	22.0±16.0	0.0–53.4	16.0±2.0	12.0–20.0
High	19.0±2.0	15.1–22.9	23.0±3.3	16.4–29.6
Tumor type				
Synovial sarcoma, NOS	16.0±1.9	12.3–19.7	16.0±2.0	12.0–20.0
Synovial sarcoma, spindle cell	22.0±3.4	15.3–28.7	23.0±3.3	16.4–29.6
Other	24.0±6.4	11.4±36.6	30.0±5.9	18.4–41.6
Tumor size				
<10 cm	29.0±5.2	18.8–39.2	33.0±4.3	24.7–41.3
≥10 cm	16.0±1.1	13.8–18.2	16.0±1.2	13.7–18.3
Surgery				
Yes	24.0±3.4	17.3–30.7	25.0±3.8	17.5–32.5
No	6.0±1.4	3.2–8.8	8.0±2.2	3.7–12.3
Radiotherapy				
Yes	22.0±2.0	18.0–26.0	22.0±2.8	16.6–27.4
No	17.0±1.7	13.7–20.3	18.0±1.6	14.9–21.1
Chemotherapy				
Yes	21.0±1.6	17.8±24.2	22.0±1.7	18.7±25.3
No	9.0±2.8	3.4±14.6	10.0±2.6	5.0±15.0

CI = confidence interval, NOS = not other specified, OS = overall survival, CSS = cancer-specific survival.

Table 3

Univariate Cox analysis of variables in patients with limb synovial sarcoma and metastasis at presentation.

	OS		CSS	
Category	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
Age, yr				
<40	1		1	
≥40	1.223 (0.907–1.649)	.188	1.225 (0.893–1.681)	.208
Gender				
Female	1		1	
Male	1.139 (0.839–1.546)	.402	1.136 (0.824–1.567)	.435
Tumor grade				
Low	1		1	
High	1.416 (0.680–2.950)	.353	1.588 (0.726–3.476)	.247
Tumor type				
Synovial sarcoma, NOS	1		1	
Synovial sarcoma, spindle cell	0.780 (0.556–1.093)	.149	0.789 (0.553–1.126)	.192
Other	0.812 (0.542–1.215)	.310	0.804 (0.522–1.236)	.320
Tumor size				
<10 cm	1		1	
≥10 cm	1.581 (1.108–2.255)	.012	1.752 (1.201–2.556)	.004
Surgery				
Yes	1		1	
No	3.299 (2.376–4.582)	<.001	3.176 (2.234–4.514)	<.001
Radiotherapy				
Yes	1		1	
No	1.365 (1.010–1.843)	.043	1.321 (0.963–1.813)	.085
Chemotherapy				
Yes	1		1	
No	1.484 (1.056–2.087)	.023	1.395 (0.963–2.201)	.078

CI = confidence interval, NOS = not other specified, OS = overall survival, CSS = cancer-specific survival.

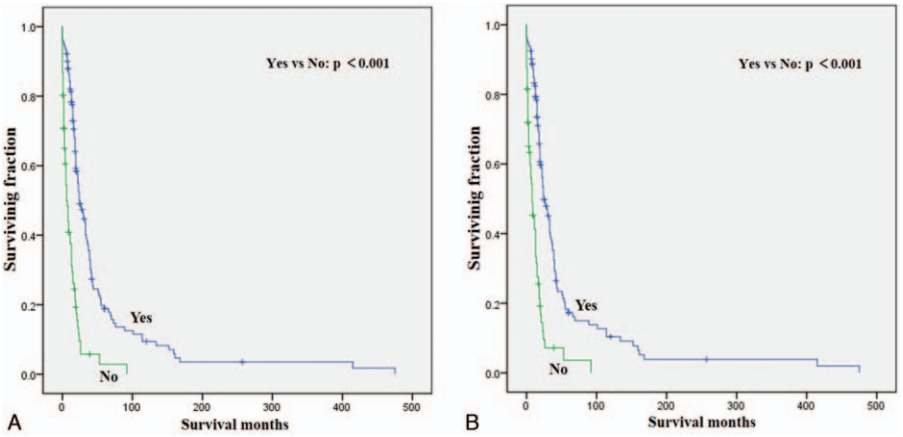

Figure 1. Kaplan–Meier plot for estimating OS (A) and CSS (B) among LSS patients with metastasis at presentation stratified by surgery. CSS = cancer-specific survival, LSS = limb synovial sarcoma, OS = overall survival.

at diagnosis (limb and trunk sites), which differed from our cohort. The survival difference in our study may be because we included only limb SS patients with metastasis at diagnosis in the survival analysis, and their study had too few patients to consider only this group. Additional studies are needed to examine this difference.

On univariate analysis, age was not a significant predictor of OS or CSS. Okçu et al[17] also found that age was not associated with survival in young SS patients. We also noted that neither gender nor tumor type was significantly related to survival. Generally, tumor grade is recognized as an important prognostic indicator in SS.[13,18] However, our univariate analysis found no obvious difference in either OS or CSS based on tumor grade. Perhaps metastatic LSS has unique features. Tumor size is one of the most significant factors associated with survival in SS.[8,17,19] Jacobs et al[19] reported that tumor size was an independent risk factor for survival in SS. Spillane et al[8] reported that tumor size was associated with the tumor stage in SS patients and affected survival. However, they also found that smaller sarcomas had an unexpectedly poor prognosis. Pappo et al[18] found a borderline significant relationship between OS and tumor size ($P = .09$), and we showed that tumor size ≥10 cm independently predicted worse survival in metastatic LSS patients.

As in many previous studies and given our sample size (n = 217), we entered only variables with $P < .1$ on the univariate analyses into the multivariate analysis. Although the univariate analyses showed that radiotherapy and chemotherapy were not associated with CSS, multivariate analysis showed these therapies were associated with CSS. Perhaps there was a correlation between radiotherapy or chemotherapy and other confounding factors that masked the true effects of radiotherapy or chemotherapy on survival. After eliminating the influence of other factors through multivariate analysis, radiotherapy or chemotherapy had independent effects on survival.

Although surgical resection is regarded as the main treatment for LSS, there is little evidence for the role of surgery in metastatic LSS. Ferrari et al[20] found that surgery alone was sufficient for patients with adequately resected SS ≤5 cm in size. We found that surgery was the most significant predictor of both OS and CSS based on multivariate analysis. Spillane et al[8] also reported that adequate local treatment affected the survival of SS patients. Adjuvant radiotherapy is often used in SS patients with tumors ≥5 cm.[17] Ferrari et al[21] thought that radiotherapy might improve local control, not only after wide resection but also after narrower resection. Al-Hussaini et al[10] showed that surgery combined with radiotherapy prolonged the survival of patients

Table 4

Multivariate Cox analysis for OS and CSS for patients with limb synovial sarcoma and metastasis at presentation.

	OS		CSS	
Category	**Hazard ratio (95% CI)**	***P*-value**	**Hazard ratio (95% CI)**	***P*-value**
Tumor size				
<10 cm	1		1	
≥10 cm	1.533(1.064–2.208)	.022	1.635 (1.103–2.425)	.014
Surgery				
Yes	1		1	
No	3.308 (2.361–4.634)	<.001	3.047 (2.121–4.376)	<.001
Radiotherapy				
Yes	1		1	
No	1.455 (1.063–1.992)	.019	1.458 (1.047–2.029)	.025
Chemotherapy				
Yes	1		1	
No	1.573 (1.094–2.262)	.014	1.478 (1.003–2.179)	.048

CI = confidence interval, OS = overall survival, CSS = cancer-specific survival.

with localized SS. This study first provided evidence for the role of radiotherapy in improving survival in metastatic LSS. Although SS is chemosensitive, the use of chemotherapy in SS is still debated.[17] Some studies reported that chemotherapy had a survival benefit in SS,[22–25] while others did not observe this.[26–28] Despite the toxicity of high-dose ifosfamide, it had a survival benefit for patients with metastatic SS.[29] Moreover, Ferrari et al[21] recommend that SS patients with tumors of >5 cm be considered first for chemotherapy. Our study made a preliminarily determination regarding the effect of chemotherapy on prolonging the survival of metastatic LSS.

There are some limitations to this study. First, the details on local or distant recurrence after diagnosis were not documented in the SEER database and might have influenced survival time. Second, clinical variables such as surgical margin, metastatic sites, treatment for metastasis, and chemoradiotherapy program were not available in this database. Future clinical studies should include these possible prognostic factors in their analyses. Third, this study was retrospective, which brings some inherent biases. Despite these limitations, the SEER database is an important tool for exploring rare tumors such as LSS patients with metastasis at presentation.

5. Conclusion

This study revealed that LSS patients with metastasis at presentation had a very poor prognosis. Combined surgery, radiotherapy, and chemotherapy may prolong their survival.

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